

## REMARKS

This is in response to the Final Office Action mailed June 26, 2003 and Applicants' telephone interview with Examiner J. A. Goldberg on October 28, 2003. Claims 2-3, 7-12, 23, 34 and 36-42 have been canceled. Claims 1, 13, 22 and 32 have been amended. Claims 1, 4-6, 13-22, 24, 33 and 35 are now pending.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

### **1. Restriction Requirement**

The Examiner has issued a restriction requirement as to 8 different inventions. Applicants' amendments to the independent claims render the restriction requirement moot because the claimed method utilizes a set of primers having specific DNA SEQ ID NOs: 1 and 2. Since all of independent claims contain such a core structural limitation, a unity of invention is preserved. Withdrawal of restriction requirement is therefore respectfully requested.

### **2. Claim Objections**

The Examiner has identified a few editorial errors in claims 1, 4-7, 10, 13, 15, and 32. Applicants amended these claims accordingly to the Examiner's suggestion.

### **2. New Matter**

The Examiner rejected claims 1, 4-6, 10, 13, 15, 22-23, 25, 32-34, and 36 for containing new matter as to the term "a first primer hybridizes under high stringency conditions to a region.....". Applicants' deletion of this term in the pending claims renders the rejection moot.

### **3. Rejections under 35 U.S.C. § 112, First Paragraph**

The Examiner rejects claims 32-36 under 35 U.S.C. § 112, First Paragraph for lack of enablement. Applicants' amendment to claim 32 and cancellation of claim 36 render the rejection moot.

#### **4. Rejections under 35 U.S.C. § 112, Second Paragraph**

The Examiner rejected claims 1, 4-6, 10, 13, 15, 22-23, and 25 under 35 U.S.C. § 112, Second Paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner rejected claims 1, 4-6, 10, 13, and 15 over the recitation “and the second primer hybridizes under high stringency conditions.....”. Applicants’ deletion of the recitation renders the rejection moot.

The Examiner also rejected claims 1, 4-7, 10, 13, 15, 22-23, 25, 32-34 and 36 over the recitation “ a mutation at amino acid position 131”. The Examiner alleged that it is unclear what is being referred to as amino acid position 131 and how position 131 relates to a sequence.

Applicants respectfully direct the Examiner’s attention to a reference by Carmen et al. (1990) Lancet 336:325-329 and cited in the IDS submitted by Applicants on March 25, 2003. According to Carmen et al. on page 328 under “Discussion”, and Figure 4 and its legend, the numbering system of amino acid sequence in HBsAg is well recognized by skilled artisans in the relevant field. Applicants’ numbering of the amino acid residue in the same region is consistent with this common numbering system, and is sufficiently definite to the skilled artisans in the relevant field of HBV virology.

The Examiner also rejected claims 22-23, and 25 for being indefinite as to the recitation “the mixture” for lacking of antecedent basis. Applicants amend independent claim 22 to recite step i) to be “mixing the sample with a set of first and second primers.....” and thus provide antecedent basis for the term “the mixture”.

In addition, the Examiner rejected claims 22-23, and 25 for being indefinite as to step iii). Applicants amended claim 22 to add step iv) of “identifying said mutation.....” by following the Examiner’s suggestion.

In view of the amendments to the claims and above remarks, Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. § 112, Second Paragraph.

## **5. Rejections under 35 U.S.C. § 102**

### **1) Over Weinberger et al.**

The Examiner rejects claims 1, 15, 22, and 25 under 35 U.S.C. § 102(b) as being anticipated by Weinberger et al. (Viral Hepatitis and Liver Disease, pp. 138-143, Torino, Edizioni Minerva Medica, 1997).

Independent claim 1 as amended specifies a primer extension amplification method for detecting mutation of HBV in a sample by using a pair of specifically designed primers having SEQ ID NOs: 1 and 2 for detecting a mutation at amino acid position 130, 131, 133 or 145, or mutations at amino acid positions 130 and 145, 130 and 133, 131 and 145, or 133 and 145.

In contrast, Weinberger et al. does not teach a method using such a pair of primers for detecting mutation at these specific amino acid positions. Thus, Weinberger et al. fails to anticipate the claimed invention. Withdrawal of the rejection under 35 U.S.C. § 102(b) is therefore respectfully requested.

### **2) Over McMahon et al.**

The Examiner rejects claims 1, 15, 22, and 25 under 35 U.S.C. § 102(b) as being anticipated by McMahon et al. (Hepatology 15:757-766, 1992).

As discussed above, independent claim 1 as amended specifies a primer extension amplification method for detecting mutation of HBV in a sample by using a pair of specifically designed primers having SEQ ID NOs: 1 and 2 for detecting a mutation at amino acid position 130, 131, 133 or 145, or mutations at amino acid positions 130 and 145, 130 and 133, 131 and 145, or 133 and 145.

McMahon et al. does not teach a method using such a pair of primers for detecting mutation at these specific amino acid positions. In contrast, the prime pair used by McMahon is distinctively different from SEQ ID NOs: 1 and 2. As shown in page 758, column 2, McMahon teaches using a 5' primer and a 3' primer having different sequence than that of SEQ ID NOs: 1 and 2. Thus, McMahon fails to anticipate the claimed invention. Withdrawal of the rejection under 35 U.S.C. § 102(b) is therefore respectfully requested.

6. **Rejections under 35 U.S.C. § 103(a)**

**1) Over Weinberger et al. in view of Mbayed et al.**

The Examiner rejects claims 10 and 23 under 35 U.S.C. § 103(a) as being unpatentable over Weinberger et al. in view of Mbayed et al (J. Clinical Microbiology 36:3362-3365, 1998).

Independent claim 1 has been amended by incorporating the limitation in claim 10 to specify a method for detecting mutation of HBV in a sample using a pair of specifically designed primers having SEQ ID NOs: 1 and 2 for detecting a mutation at amino acid position 130, 131, 133 or 145, or mutations at amino acid positions 130 and 145, 130 and 133, 131 and 145, or 133 and 145.

As acknowledged by the Examiner, Weinberger et al does not specifically teach using primers of SEQ ID NOs: 1 and 2; neither does the cited secondary reference, Mbayed et al. Mbayed et al. teaches a method of amplifying part of the surface antigen of HBV using 2 pairs of primers: primer 163/primer 376, and primer HBS1/ primer HBS2. Although SEQ ID NO: 1 shares some sequence identity with that of primer HBS1, none of these 2 **primer pairs** have the same sequence as that of the SEQ ID NOs: 1 and 2. Thus, the cited references, each alone or in combination, fail to teach the claimed method using a specifically designed pair of primers having SEQ ID NOs: 1 and 2.

To establish a prima facie case of obviousness, 1) the prior art reference (or references when combined) **must teach or suggest all the claim limitations**; 2) the prior art must contain a **suggestion or motivation to combine** the prior art references in such a way as to achieve the claimed invention; and 3) one of ordinary skill in the art at the time the invention was made would **have reasonable expectation of success** of the claimed invention. Emphasis added, *In re Vaeck*, 947 F. 2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); *In re O'Farrell*, 853 F. 2d 894, 903-904, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988); and *In re Dow Chem.*, 837 F. 2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

Weinberger's teaching of using primers to target HBV genome in general does not teach or suggest that the primer pairs disclosed therein should be modified to have the same sequence as SEQ ID NOs: 1 and 2. Further, Mbayed's teaching of a primer pair that targets a different region of the HBV does not give a clue as to how Weinberger's primer pairs should be modified to arrive the claimed method using the specifically designed primer pair of SEQ ID NOs: 1 and 2.

In addition, one of ordinary skill in the art would not have reasonable expectation of success of the claimed invention, considering the unpredictable nature of biotechnology.

However, in the Summary of Interview mailed November 5, 2003, the Examiner asserted that the primers SEQ ID NOs: 1 and 2 are functional equivalents to the primers taught by Mbayed et al. Relying on *in re Deul* [sic] but failing to show the exact citation of this case, the Examiner concluded that the primers SEQ ID NOs: 1 and 2 are thus prima facie obvious in view of Mbayed et al. Applicants disagree with the Examiner's assertion and request the Examiner to provide the exact citation of *in re Deul* to show where the court reasoned/decided that a primer pair having different sequences is per se a functional equivalent to another pair of primers, and to provide objective evidence showing why the SEQ ID NOs: 1 and 2 are functional equivalent of those in Mbayed et al.

Contrary to the Examiner's assertion, pursuant to the MPEP 2144.08 II A 4(a), "the mere fact that a prior art genus contains a small number of members does not create a *per se* rule of obviousness. Some motivation to select the claimed species or subgenus must be taught by the prior art. See, e.g., *Deuel*, 51 F.3d at 1558-59, 34 USPQ2d at 1215 ("No particular one of these DNAs can be obvious unless there is something in the prior art to lead to the particular DNA and indicate that it should be prepared.")". Thus, absent any objective evidence showing that the primers in Weinberger et al. should be modified in view of Mbayed's teaching, a prima facie case of obviousness has not been established. Withdrawal of this ground of rejection is respectively requested.

## **2) Over Weinberger et al. in view of Mason et al.**

The Examiner reject claims 4 under 35 U.S.C. § 103(a) as being unpatentable over Weinberger et al. in view of Mason et al.

As discussed in detail above, independent claim 1 as amended specifies a method for detecting mutation of HBV in a sample using a pair of specifically designed primers having SEQ ID NOs: 1 and 2 for detecting a mutation at amino acid position 130, 131, 133 or 145, or mutations at amino acid positions 130 and 145, 130 and 133, 131 and 145, or 133 and 145.

As acknowledged by the Examiner, Weinberger et al does not specifically teach using primers of SEQ ID NOs: 1 and 2; neither does the cited secondary reference, Mason et al.

The cited references, each alone or in combination, fail to teach or suggest using such specifically designed and unique primers to detect mutation at these specific amino acid positions. A prima facie case of obviousness has not been established under 35 U.S.C. § 103(a). Withdrawal of this ground of rejection is respectfully requested.


**CONCLUSION**

Applicants earnestly believe that they are entitled to a letters patent, and respectfully solicit Examiner to expedite prosecution of this patent application to issuance. Should Examiner have any questions, the Examiner is encouraged to telephone the undersigned.

Respectfully submitted,

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